



MAIL STOP APPEAL BRIEF-PATENTS  
PATENT  
2001-1028

IN THE U.S. PATENT AND TRADEMARK OFFICE BEFORE  
THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	Appeal No.
Marinus Gerardus Cornelis KIVITS et al.	Conf. 5816
Application No. 10/089,995	Group 1647
Filed July 25, 2007	Examiner S. Shafer

# PROCESS FOR OBTAINING GROWTH FACTOR PREPARATIONS (TGF-BETA AND IGF-1) FROM MILK PRODUCTS HAVING LOW MUTUAL CROSS-CONTAMINATION

APPEAL BRIEF

MAY IT PLEASE YOUR HONORS:

(i) **Real Party in Interest**

The real party in interest in this appeal is CAMPINA B.V. of Zaltbommel, The Netherlands.

(ii) **Related Appeals and Interferences**

None.

(iii) Status of Claims

Claims 16-23 and 33-35 are pending. Claims 16-23 and 33-35 stand rejected in the "Final" Official Action mailed February 26, 2007. The rejection of claims 16-23 and 33-35 is the subject of this appeal. Claims 1-15 and 24-32 have been canceled.

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(iv) **Status of Amendments**

An Amendment After Final Rejection was filed in conjunction with this Appeal Brief canceling claims 24-32.

(v) **Summary of Claimed Subject Matter**

The claimed invention is a process for obtaining from milk product relatively pure fractions of transforming growth factor (TGF- $\beta$ ), insulin-like growth factor (IGF-1), and optionally lactoperoxidase (pg. 3, lines 14-20). TGF- $\beta$  and IGF-1 are growth factors that regulate a variety of cellular processes and have several potential therapeutic applications (pg. 1, lines 24-29 and pg. 2, lines 5-14). Lactoperoxidase is an enzyme which may be used as a natural preservative (pg. 3, lines 10-12).

Claims 16 and 33 are the independent claims subject to appeal. Claim 16 recites a process for extracting TGF- $\beta$  and IGF-1 from a milk product, comprising the steps of

a) recovering a basic fraction from the milk product by cationic exchange chromatography (pg. 4, line 31 to pg. 5, line 29);

b) passing the fraction obtained in step a) over a hydroxyapatite column (pg. 5, line 30 to pg. 6, line 5);

c) eluting the hydroxyapatite column sequentially with at least two eluents of increasing salt concentration or pH, the eluents being selected from phosphate buffers, sodium chloride solutions and potassium chloride solutions, wherein the first

eluent has a pH of 5.5 to 7 and a salt concentration of 0.05 to 0.2 M and the second eluent has a pH of 5.5 to 7 and a salt concentration of 0.2 to 0.3 M, to obtain two separate fractions (pg. 6, lines 12-24), namely:

i) a fraction comprising IGF-1, wherein the ratio IGF-1 to TGF- $\beta$  is greater than 10:1 (pg.7, lines 14-16);

ii) a fraction comprising TGF- $\beta$ , wherein the ratio TGF- $\beta$  to IGF-1 is greater than 5:1 (pg.7, lines 21-22).

Claim 33 is a process for extracting TGF- $\beta$  and IGF-1 from a milk product, comprising the steps of

a) passing the milk product at a surface velocity of more than 500 cm per hour and a liquid load of 100-600 bed volumes per hour through a column packed with the cationic exchange resin having a mean particle size of 100-300  $\mu$ m and eluting the cationic exchange resin column with a solution to recover a basic fraction from the milk product (pg. 5, lines 15-19 and pg.7, lines 21-22);

b) passing the fraction obtained in step a) over a hydroxyapatite column (pg. 5, line 30 to pg. 6, line 5);

c) eluting the hydroxyapatite column sequentially with at least two eluents of increasing salt concentration or pH, the eluents being selected from phosphate buffers, sodium chloride solutions and potassium chloride solutions, wherein the first eluent has a pH of 5.5 to 7 and a salt concentration of 0.05 to 0.2 M and the second eluent has a pH of 5.5 to 7 and a salt

concentration of 0.2 to 0.3 M, to obtain two separate fractions (pg. 6, lines 12-24), namely:

i) a fraction comprising IGF-1, wherein the ratio IGF-1 to TGF- $\beta$  is greater than 10:1 (pg.7, lines 14-16);

ii) a fraction comprising TGF- $\beta$ , wherein the ratio TGF- $\beta$  to IGF-1 is greater than 5:1 (pg.7, lines 21-22).

The claimed invention thus reflects the inventors' discovery that the claimed column chromatography steps can be used to produce relatively pure fractions of TGF- $\beta$ , IGF-1 and lactoperoxidase.

(vi) **Grounds of Rejection to be Reviewed on Appeal**

i) The sole issue on appeal is whether claims 16-23 and 33-35 satisfy the enablement requirement under 35 USC §112, first paragraph.

(vii) **Arguments**

CLAIMS 16-23 AND 33-35 SATISFY THE ENABLEMENT REQUIREMENT

The claimed invention, which is admittedly novel and non-obvious process steps, is fully enabled by the present disclosure. In particular, the specification provides ample guidance to one skilled in the art as to the selection of the eluent buffers, salt concentrations and pH levels needed to practice the claimed invention.

The Final Official Action essentially contends that the claimed process must recite specific eluent buffers, salt concentrations and pH levels (see Final Official Action top of pg. 4) disclosed as preferred embodiments in the present specification because the claimed process results in fractions of TGF- $\beta$  and IGF-1 having specifically identified characteristics.

However, as to the step of eluting a basic fraction, both independent claims 16 and 33 recite recovering a basic fraction from a milk product via cationic exchange chromatography. Claim 33 also recites what type of resin is used and how the cationic exchange chromatography column is loaded. Thus, with this information alone, one skilled in the art would select a suitable buffer, salt concentration, and pH level suitable for recovering a basic fraction from a milk product by cationic exchange chromatography.

However, the specification provides even further guidance by disclosing preferred type of resins (pg. 5, lines 1-4) and preferred process parameters such as type of eluent buffers, salt concentrations and pH levels that may be used (pg. 5, lines 6-14; pg. 5, lines 15-23; pg. 5, lines 21-23; and pg. 5, lines 25-30). The specification also refers to United States Patent No. 5,596,082 as providing guidance (pg. 5, line 18).

One skilled in the art would also be able to elute the hydroxyapatite column sequentially with at least two eluents of increasing pH concentrations. Both independent claims 16 and 33

expressly recite that the first and second eluents have a pH of 5.5 to 7. Thus, the claims already provide guidance as to the initial pH concentrations that are used to practice the claimed invention. Furthermore, the specification does provide further guidance as to the preferred type of resins (pg. 6 lines 1-5) and process parameters of hydroxyapatite resins that may be used (pg. 6, lines 12-17 and pg. 6, lines 19-24).

Although the Final Official Action notes that a shift to a pH from 5.5 to 7.0 represents a 50-fold decrease in hydrogen ion concentration, this observation does not provide any insight into whether one skilled in the art could practice the claimed invention. Rather, the question is whether one skilled in the art would be able to select eluents with the appropriate pH so as to be able to elute a hydroxyapatite column sequentially with at least two eluents of increasing pH concentrations as claimed. In light of the pH values already recited in the claims and the teachings of the specification, one skilled in the art would plainly be able to accomplish this task.

As to eluting the hydroxyapatite column with a third eluent having increased salt content or pH as compared to the first and second eluents, one skilled in the art would take into consideration the salt concentrations and pH already utilized in the first two buffers. Furthermore, dependent claims 17 and 35, which recite this embodiment, expressly recite the type of buffer eluent that should be used for the eluent. Thus, one skilled in

the art is provided sufficient guidance so as to be able to elute the hydroxyapatite column with a third eluent having increased salt content or pH as compared to the first and second eluents.

Thus, upon considering the recitations of the claims and embodiments disclosed as preferred embodiments set forth in the specification, one skilled in the art would be able to practice the claimed invention in its entirety. In determining whether an unclaimed feature is critical, the entire disclosure must be considered. Features which are merely preferred are not to be considered critical. In re Goffe, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976). As none the embodiments identified by the Final Official Action are characterized as essential to practicing the claimed invention and would be identified as preferred embodiments by one skilled in the art for the reasons noted above, it is believed that the enablement rejection is improper as a matter of law.

It is true that independent claims 16 and 33 recite that two separate fractions having "specifically identified characteristics" are obtained:

- i) a fraction comprising IGF-1, wherein the ratio IGF-1 to TGF- $\beta$  is greater than 10:1; and
- ii) a fraction comprising TGF- $\beta$ , wherein the ratio TGF- $\beta$  to IGF-1 is greater than 5:1 (pg.7, lines 21-22).

However, in that these two fractions must be obtained, it is believed that the recitations provide further guidance to

one skilled in that art as how to practice the claimed invention. Any process parameters or conditions that did not provide these "specifically identified characteristics" would be excluded from the claims.

In support of the rejection, the Official Action of June 30, 2006 cites to several publications (e.g., BELFORD et al., KUSSENDRAGER et al., and QUINQUE) that discuss eluting growth factors. The Official Action concludes that these publications provide evidence that the claimed process must recite specific eluent buffers, salt concentrations and pH levels because the publications themselves disclose specific eluent buffers, salt concentrations and pH levels. However, none of the publications cast doubt as to whether the claimed process is enabled. Indeed, the Official Action even acknowledges that the publications are distinct from the claimed invention (see Official Action of June 30, 2006, pg. 8). Rather, appellants believe that the publications actually show that one skilled in the art would know or be able to select the buffers, salt concentrations and pH levels needed to practice the claimed invention.

In this regard, appellants submit that the Official Action fails to satisfy its burden in showing that claims 16, 18-23, and 33-34 do not satisfy the enablement requirement. It is a well-founded principle that any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with



the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed.

As a matter of law, the expressed teaching of the patent specification cannot be controverted by mere speculation and unsupported assertions on the part of the Patent Office. As stated by the Court of Customs and Patent Appeals in the case of *In re Dinh-Nguyen and Stanhagen*, 181 USPQ 46 (CCPA 1974):

Any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. 181 USPQ at 47.

Such a standard must be applied with great care when the Examiner's conjecture is contrary to the teachings of the specification.

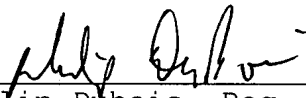
In that one skilled in the art would know or be able to select the eluent buffers, salt concentrations and pH levels needed to practice the claimed invention and the Final Official Action provides no evidence to the contrary, it is believed that claims 16-23 and 33-35 satisfy the enablement requirement under 35 USC §112, first paragraph.

Conclusion

From the foregoing, it is believed to be apparent that the enablement rejection does not merit affirmance by the Board, but rather that the enablement rejection should be reversed. Such action is accordingly respectfully requested.

Respectfully submitted,

YOUNG & THOMPSON

  
\_\_\_\_\_  
Philip Dubois, Reg. No. 50,696  
745 South 23<sup>rd</sup> Street  
Arlington, VA 22202  
Telephone (703) 521-2297  
Telefax (703) 685-0573  
(703) 979-4709

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August 16, 2007

**Claims Appendix**

16. A process for extracting transforming growth factor  $\beta$  (TGF- $\beta$ ) and insulin-like growth factor 1 (IGF-1) from a milk product, comprising the steps of

a) recovering a basic fraction from the milk product by cationic exchange chromatography;

b) passing the fraction obtained in step a) over a hydroxyapatite column;

c) eluting the hydroxyapatite column sequentially with at least two eluents of increasing salt concentration or pH, said eluents being selected from phosphate buffers, sodium chloride solutions and potassium chloride solutions, wherein the first eluent has a pH of 5.5 to 7 and a salt concentration of 0.05 to 0.2 M and the second eluent has a pH of 5.5 to 7 and a salt concentration of 0.2 to 0.3 M, to obtain two separate fractions:

i) a fraction comprising IGF-1, wherein the ratio IGF-1 to TGF- $\beta$  is greater than 10:1;

ii) a fraction comprising TGF- $\beta$ , wherein the ratio TGF- $\beta$  to IGF-1 is greater than 5:1.

17. The process according to claim 16, further comprising a step of

d) eluting the hydroxyapatite column with a third eluent having increased salt content or pH as compared to the first and second eluents used in step c), said third eluent being

selected from the group consisting of phosphate buffers, sodium chloride solutions and potassium chloride solutions to obtain iii) a fraction comprising lactoperoxidase.

18. The process according to claim 17, wherein the eluent for obtaining fraction iii) has a pH of 5.5 to 8 and a salt concentration of 0.3 to 0.5 M.

19. The process according to claim 16, wherein said eluents are phosphate buffers.

20. The process according to claim 16, wherein step a) is carried out by passing the milk product at a surface velocity of more than 500 cm per hour and a liquid load of 100-600 bed volumes per hour through a column packed with the cationic exchange resin having a mean particle size of 100-300  $\mu$ m.

21. The process according to claim 16, wherein the milk product is any mammalian milk.

22. The process according to claim 21, wherein the milk product is cheese whey.

23. The process according to claim 21, wherein the fat has been removed from the mammalian milk.

33. A process for extracting transforming growth factor  $\beta$  (TGF- $\beta$ ) and insulin-like growth factor 1 (IGF-1) from a milk product, comprising the steps of

a) passing the milk product at a surface velocity of more than 500 cm per hour and a liquid load of 100-600 bed volumes per hour through a column packed with the cationic exchange resin having a mean particle size of 100-300  $\mu$ m and eluting the cationic exchange resin column with a solution to recover a basic fraction from the milk product;

b) passing the basic fraction obtained in step a) over a hydroxyapatite column;

c) eluting the hydroxyapatite column sequentially with at least two eluents of increasing salt concentration or pH, said eluents being selected from phosphate buffers, sodium chloride solutions and potassium chloride solutions, wherein the first eluent has a pH of 5.5 to 7 and a salt concentration of 0.05 to 0.2 M and the second eluent has a pH of 5.5 to 7 and a salt concentration of 0.2 to 0.3 M, to obtain two separate fractions:

i) a fraction comprising IGF-1, wherein the ratio IGF-1 to TGF- $\beta$  is greater than 10:1;

ii) a fraction comprising TGF- $\beta$ , wherein the ratio TGF- $\beta$  to IGF-1 is greater than 5:1.

34. The process according to claim 18, wherein the milk product is any mammalian milk.

35. The process according to claim 34, further comprising a step of

d) eluting the hydroxyapatite column with a third eluent having increased salt content or pH as compared to the first and second eluents used in step c), said third eluent being selected from the group consisting of phosphate buffers, sodium chloride solutions and potassium chloride solutions to obtain  
iii) a fraction comprising lactoperoxidase.

(ix) **Evidence Appendix**

None.

(x) **Related Proceedings Appendix**

None.